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ORIGINAL ARTICLE

Dyslipidemia Associated with Poor Glycemic Control in Type 2 Diabetes Mellitus and the Protective Effect of Metformin Supplementation

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Abstract The nature of the dyslipidemia associated with diabetes mellitus is complex and is the major risk factor for atherosclerosis and coronary artery disease. Aim of this study was to assess the effect of glycemic control, achieved by metformin, glibenclamide and insulin, on lipid profile in type 2 diabetic patients. One hundred and sixty-five type 2 diabetes mellitus patients were classified into good glycemic control (Group I) and poor glycemic control (Group II) on the basis of their blood HbA1c values. The Group II was characterized with high serum triglyceride (190.46 ± 15.20 mg/dl), total cholesterol (175.3 ± 6.31 mg/dl) as well as high LDL-cholesterol (109.0 ± 5.88 mg/dl). Significant correlations were evident between HbA1c and dyslipidemia, particularly serum TG ($r = 0.28$, $P < 0.05$), and between HbA1c and total cholesterol ($r = 0.310$, $P < 0.05$). Better glycemic control and improved dyslipidemia were observed in patients on combination therapy of metformin plus glibenclamide.

Keywords Diabetes mellitus · Glycemic control · HBA1c · Dyslipidemia · Metformin · Glibenclamide

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Introduction

Diabetes mellitus, initially considered a carbohydrate metabolic disease, is now described as a disorder of multiple etiologies with disturbances of carbohydrate, lipid as well as protein metabolism. Population growth, urbanization, and increasing prevalence of obesity and physical inactivity are the major risk factors contributing to the increasing prevalence of type 2 diabetes (T2DM). Over the next two decades, the largest increase in the number of people with diabetes will be seen in developing countries, particularly in people of working age [1]. Complications of T2DM are mainly associated with diabetic vasculopathy, which are commonly grouped into two categories, viz., microvascular (retinopathy, neuropathy and nephropathy) and macrovascular (which puts the diabetic patients at increased risk of cardiovascular disease). The overall temporal burden of hyperglycemia is responsible for diabetic complications and adverse outcomes [2]. Although, with the advances in medical practice and technology, the overall risk of mortality from the cardiovascular disease has decreased, the diabetes mellitus patients continue to display distressingly high morbidity and mortality due to coronary events [3]. The increased vascular risk associated with T2DM is likely to be multifactorial, but dyslipidemia, now called as '*diabetes lipidus*', plays an important role [4]. It is important to note that dyslipidemia in diabetic patients is more atherogenic than that in non-diabetics.

The WHO model list of essential medicines [5] lists two oral hypoglycemic drugs for management of diabetes mellitus. Glibenclamide (belonging to class sulfonylureas) is an established oral hypoglycemic, whereas metformin (from biguanide class) is relatively new addition to the common regimen. It has become tremendously popular, and the choice of drug for management of T2DM, owing to

its hypoglycemic as well as hypolipidemic effects. The increase in triglycerides in T2DM is accompanied by pro-atherosclerotic functional changes in HDL and LDL particles [6] and metformin affects a reduction in LDL cholesterol as well as triglyceride levels in blood and hence could be protective against the effects of dyslipidemia [7]. It is the only antidiabetic drug that has been conclusively shown to prevent the cardiovascular complications of diabetes and does not cause weight gain. The mechanism of action of metformin appears to be through stimulation of AMP dependent protein kinase (AMPK) activity. The active kinase then favours the peripheral utilization of glucose and mobilization of glycogen in muscle tissue [8].

The present study was planned to investigate the effect of glycemic control on dyslipidemia associated with type 2 diabetes mellitus and to explore the efficacy of metformin on glycemic control and reversal of diabetes lipidus.

Materials and Methods

Patients

This study was conducted on the type 2 diabetic out patients attending the diabetes clinic of Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia. One hundred and sixty-five consecutive patients with a minimum five years history of type 2 diabetes mellitus were recruited for the study after obtaining the informed consent. Majority (61.5 %) of the patients were stabilized on i/p insulin, 21.5 % were on glibenclamide alone and 17 % were on combination of glibenclamide plus metformin.

Glycemic Control

Blood samples were collected after an overnight fast and before the morning insulin injection or oral glycemic control therapies.

(a) Glucose—Blood glucose in the venous blood was determined by glucose oxidase method using the commercial kits supplied by Fluitest® GLU, Germany.
(b) Total Haemoglobin—Concentration of total haemoglobin in blood was determined by the method of Zander et al. [9].
(c) Glycosylated haemoglobin (HbA1c) levels were determined by a standard latex enhanced turbidimetric immunoassay kit from Spinreact Inc., Spain. The kit is based on the method given by Metus et al. [10].

The study subjects were categorized into two groups based on their HbA1c level as Group I (good glycemic control, HbA1c < 8 g %) and Group II (poor glycemic control, HbA1c ≥ 8 g %) groups.

Dyslipidemia

The assessment of dyslipidemia was based on estimation of various lipid parameters in the fasting venous blood, viz., serum triglyceride, total cholesterol, HDL-cholesterol and LDL-cholesterol. All these parameters were done using standard methods by commercial kits as mentioned below.

(1) Serum triglycerides was estimated by using the commercial kit (Lot-12284) obtained from Cromatest® Cholesterol MR, Linear Chemicals SL, Barcelona, Spain.
(2) Total cholesterol was estimated by using the commercial kit (Lot-12284) obtained from Cromatest® Cholesterol MR, Linear Chemicals SL, Barcelona, Spain.
(3) HDL-cholesterol in the patient's blood samples was estimated by using the commercial kit (Lot-12284) obtained from Cromatest® Cholesterol MR, Linear Chemicals SL, Barcelona, Spain.
(4) The method involves measurements of fasting plasma total cholesterol, triglyceride, and high-density lipoprotein cholesterol concentrations and calculating the value of LDL-C by using Friedewald's formula.

Data Analysis

Data generated as above was analysed using SPSS ver. 16.0 statistical package.

Results

Study Subjects

The study cohort included 68 male and 97 female subjects with an average age of 56.8 $\pm$ 1.5 years. The mean duration (after diagnosis) of the disease of the study subjects was 13.20 $\pm$ 1.07 years, respectively.

Glycemic Control

In spite of the regular medical management, most of the patients (70.8 %) were found to have poor glycemic control, i.e., were having HbA1c more than 8.0 g %. Poor glycemic control was more prevalent in the patients managed by single drug therapy (75 and 71.5 % in patients on insulin or glibenclamide, respectively) compared to those maintained on metformin plus glibenclamide (54.5 %). The average glycemic control as reflected by Mean HbA1c values was also better with the combination therapy (Table 1).

Table 1 HbA1c values (mean ± SEM) and per cent of patients maintaining poor glycemic control (Group II) in the mono-therapy and combination therapy groups

	HbA1c (g %)	Subjects in Group II (%)
Insulin	9.36 ± 0.29	75.0
Glibenclamide	9.69 ± 0.67	71.4
Glibenclamide + metformin	8.38 ± 0.51	54.5

Diabetes Lipidus

Triglycerides

As shown in Fig. 1a, the triglyceride concentration (mean ± SEM) in Group I (190.46 ± 15.20 mg/dl) was significantly higher than that in Group II (132.05 ± 14.19 mg/dl).

The glycemic control in T2DM patients appears to have a direct effect on the lipid profile. A significant positive correlation (correlation coefficient $r = 0.28$, $P < 0.05$) was seen between the serum triglyceride concentrations and HbA1c values (Fig. 1b). The patients with good glycemic control showed moderately high levels of triglycerides, the maximum being 290 mg/dl. The poor control patients, on the other hand, had more varied triglyceride levels and reached a maximum of 516 mg/dl. Hypertriglyceridemia (defined as TG > 150 mg/dl), was observed in 52.3 % of the study subjects. A higher proportion (58.7 %) of the Group II patients showed hypertriglyceridemia, compared to 36.8 % in Group I. Among the subjects with high triglycerides, majority (79.4 %) were not maintaining their glucose well.

Cholesterol

When the cholesterol levels were compared between the two groups (Fig. 2), the Group I showed lower cholesterol values than that observed in the subjects with Group II. The mean ± SEM in the two groups was 147.0 ± 11.89 (mg/dl) and 175.3 ± 6.31 (mg/dl), respectively and the difference between the two groups was statistically significant ($P = 0.026$). Hypercholesterolemia (defined as TC > 240 mg/dl) was observed in 9.2 % of the patients in our study. Good glycemic control appeared to have direct bearing on hypercholesterolemia—89.5 % of the Group I patients had serum cholesterol below 200 mg/dl, compared to 69.6 % in Group II. A significant positive correlation (correlation coefficient $r = 0.310$, $P < 0.05$) was also seen between total cholesterol and the HbA1c values (Fig. 2b).

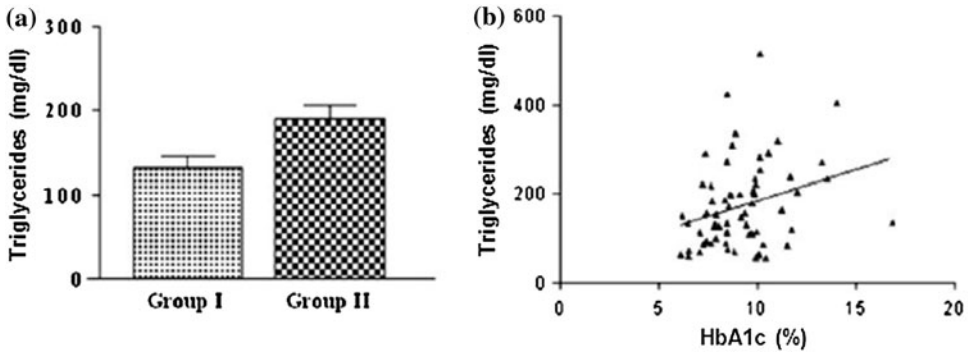

Fig. 1 Relationship of serum triglyceride levels with glycemic control. **a** Serum triglycerides (mean ± SEM) in the good and poor glycemic control groups, **b** correlation on serum trigylcerides with HBA1c

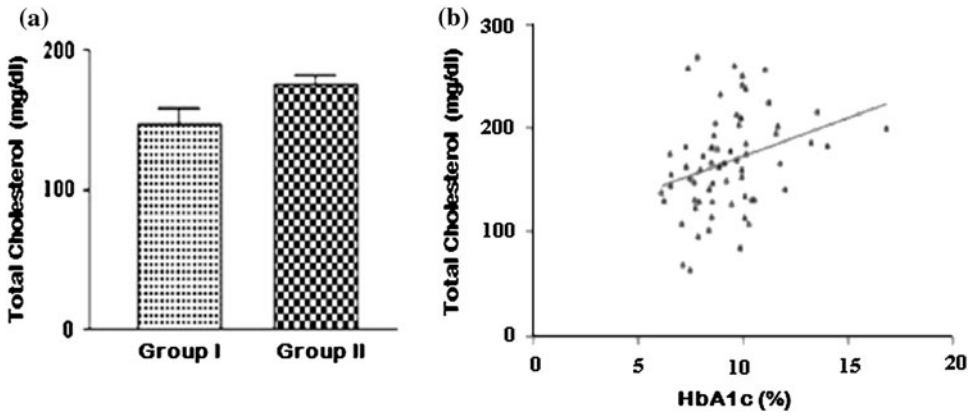

Fig. 2 Relationship of serum cholesterol levels with glycemic control. **a** Total cholesterol (mean ± SEM) in the good (Group I) and poor (Group II) glycemic control subjects, **b** correlation on serum cholesterol with HBA1c

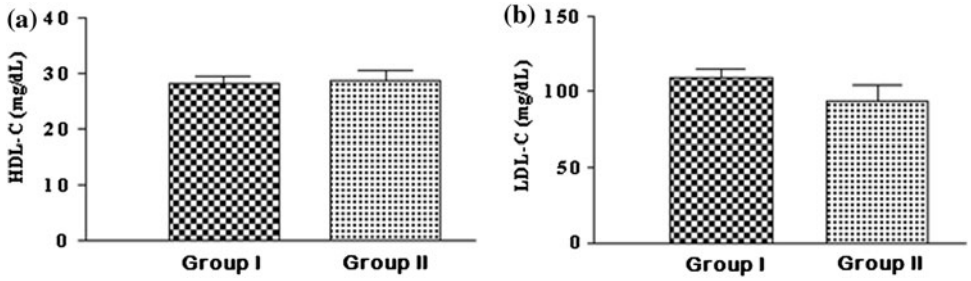

Fig. 3 Mean ± SEM serum HDL-C (**a**) and LDL-C (**b**) levels in the two glycemic groups

HDL-Cholesterol

The analysis of the HDL-cholesterol values in the two groups is presented in Fig. 3. The mean ± SEM of HDL-C in the two groups were comparable i.e. 28.24 ± 1.30 (mg/dl) and 28.62 ± 1.85 (mg/dl), respectively. Glycemic control as such did not appear to have much effect on the HDL-cholesterol levels in the present study.

LDL-Cholesterol

Mean serum LDL-C (Fig. 3) was higher in Group II diabetic patients (109.0 ± 5.88 mg/dl) compared to that in the Group I patients (93.47 ± 10.95 mg/dl). There appeared to be a non-significant positive correlation between LDL-cholesterol and the HbA1c levels ($r = 0.22$).

Effect of Hypoglycemic Therapy on Dyslipidemia

Higher cholesterol concentrations (175.00 ± 16.7 mg/dl) were found in the patients on monotherapy, i.e., taking glibenclamide only (Table 2). The patients on Insulin therapy appeared to have slightly lower cholesterol levels but addition of metformin to the management protocol resulted in a significant improvement in the serum cholesterol. The metformin not only decreased the total cholesterol levels but also had a positive effect on the distribution of cholesterol between HDL (increase) and LDL lipoproteins (decrease).

The diabetic patients on glibenclamide mono-therapy appeared to have the lowest HDL-cholesterol values (Table 2). Addition of metformin to the drug protocol raised the average HDL-cholesterol from 26.08 ± 1.90 mg/dl in glibenclamide group to 31.78 ± 8.0 mg/dl in the patients on combination therapy. The patients on insulin therapy also showed higher HDL-cholesterol values compared to that of glibenclamide mono-therapy group. Serum LDL-cholesterol levels were observed to decrease concomitant to the increase in HDL-cholesterol (from 112.44 ± 16.52 to 93.21 ± 11.85 mg/dl) upon addition of metformin to the protocol. The patients on insulin therapy showed LDL-cholesterol levels lower than that in glibenclamide mono-therapy group but higher than glibenclamide plus metformin therapy.

Discussion

Subjects with type 2 diabetes have higher cardiovascular risk than non-diabetics and the higher risk for macrovascular complications cannot be explained solely by abnormal levels of conventional cardiovascular risk factors [11]. The increased vascular risk appears to be multifactorial, but dyslipidemia is likely to play an important role [12].

Diabetic Dyslipidemia

The features of dyslipidemia can be highly varied, however, the most common phenotype is high triglyceride concentration, low HDL cholesterol and high LDL-cholesterol, particularly small dense particles [13]. The diabetes state itself, particularly hyperglycemia, is likely to contribute to excessive cardiovascular risk in patients with type 2 diabetes. Therefore, intensive glycemic control in DM patients may lead to overall improvement of the lipid profile of the patients and hence reduction in the associated cardiovascular risk. Various studies done on glycemic control and lipid profile abnormalities in type 1 diabetic patients have shown that improvement of glycemic control improves most of the components of diabetic dyslipidemia.

Table 2 Comparative lipid profiles of patients on mono- and combination therapy

Therapy	Total cholesterol (mg/dl)	HDL-cholesterol (mg/dl)	LDL-cholesterol (mg/dl)
Insulin	166.20 ± 7.07	30.60 ± 1.69	102.38 ± 5.84
Glibenclamide	175.00 ± 16.7	26.08 ± 1.90	112.44 ± 16.52
Glibenclamide + metformin	159.91 ± 10.17	31.78 ± 8.0	93.21 ± 11.85

There has been considerable debate as to whether these findings can be extrapolated to patients with type 2 diabetes, because risk factors for complications may differ between type 1 and type 2 diabetes.

The present study shows that most (70.8 %) of the patients maintained a poor glycemic control with a mean ± SEM HbA1c value of 9.27 ± 0.25. These results show that the glycemic control of the type 2 diabetic patients in African countries is quite poor [14] and 75 % of the diabetic patients require admissions during their life time directly or indirectly due to uncontrolled diabetes. Dyslipidemia (diabetes lipidus) was observed in a number of patients, e.g., as many as 52.3 % of subjects showed hypertriglyceridemia, and 39.2 % also had hypercholesterolemia. The Framingham Heart Study [15] was the first extensive work that established dyslipidemia as a constant feature in type 2 diabetes. The study reported a significantly higher prevalence of dyslipidemia in diabetic patients compared to the non-diabetic individuals. Siraj et al. [16] reported prevalence of hypercholesterolemia as 47.3 % and hypertriglyceridemia as 41.8 % in type 2 diabetic patients.

Our study demonstrated that patients with poor glycemic control (Group II) have higher serum TG level than those with good glycemic control (Group I), i.e., the diabetes lipidus is directly affected by the management of hyperglycemia. Abdel-Gayoum [17] reported that improvement in glycemic control in T2DM patients results in a lower serum TG level. The higher plasma TG is a predictor of CAD and triglycerides enhances the binding of monocytes to endothelial cells [18]. Guerci et al. [19] have also demonstrated that the endothelial dysfunction of type 2 diabetics is linked to the triglyceride enrichment of VLDL and LDL. We observed a positive and significant correlation ($r = 0.28$, $P < 0.05$) between serum TG levels and HbA1c in our patients, i.e., the poor glycemic control appeared to be directly associated with hypertriglyceridemia. Although, increased free fatty acids (FFA) released from insulin resistant tissues is a major factor in causation of the diabetes lipidus, acute hyperglycemia is also found to increase plasma TG by stimulating hepatic TG secretion, in a manner independent of either plasma insulin or free fatty acids levels [20].

In the present study, a large number of patients could be ascribed to high risk category for CAD because of high total cholesterol levels accompanied by a pronounced serum LDL-cholesterol and most (90.6 %) of the group showed lower serum HDL-cholesterol values. The mean total cholesterol values between poor and good glycemic control groups showed a significant difference, furthermore HbA1c values were also found to correlate with total cholesterol. A study by Fujita et al. [21] showed a statistically significant improvement in total cholesterol value with improved glycemic control.UK Prospective Diabetes Study [22] has shown similar findings, where low HDL cholesterol was found to be almost twice as prevalent in the diabetic patients as in the non-diabetics. Seraj et al. [16] emphasized the importance of glycemic control in diabetes patients and reported hyperglycemia related lower HDL-C values. The diabetes lipidus was much more pronounced in Group II compared to those who maintained good glycemic control (Group I). The direct relationship of glycemic control with dyslipidemia has also been confirmed by Mohammadi et al. [23], who observed that the Triglycerides, LDL-cholesterol, and total serum lipids levels of poorly controlled diabetic children (HbA1c > 8 %), were, respectively, higher than those of the control group. HDL-cholesterol level was significantly lower ($P < 0.01$) in poorly diabetic children than in control group.

The mechanism of dyslipidemia in type 2 diabetes has been explained on the basis of insulin resistance that distorts the lipoprotein lipase to hepatic lipase ratio resulting in decreased HDL-cholesterol levels. Depletion in cholesteryl esters from HDL is primarily due to increased activity of cholesterol ester transfer protein (CETP) that finally culminates in lowered HDL-cholesterol [24]. The mechanism of increase in triglyceride levels in hyperglycemic subjects also involves reduction of lipoprotein lipase (LPL) activity. It has been documented that LPL activity is lower in patients with type 2 diabetes mellitus [25]. LPL hydrolyses triglycerides of chylomicrons and very low density lipoproteins (VLDL). The FFA flux into glycogen rich hepatocytes triggers triglyceride synthesis, which in turn stimulates synthesis and secretion of VLDL-cholesterol [26]. By analysing laboratory data from 2,200 type 2 diabetic patients, Khan [27] showed that HbA_{1c} had a direct and significant correlations with cholesterol, triglycerides and LDL and inverse correlation with HDL. He suggested that HbA_{1c} can provide valuable supplementary information about the extent of circulating lipids besides its primary role in monitoring long-term glycemic control. LDL cholesterol and atherosclerosis are related in diabetic and non-diabetic subjects; however, the former are more prone to atheroma formation compared to the latter with similar LDL-C [21]. In this study, the mean LDL-C level in Group II was found to be higher than that in the Group I, although the difference was not statistical significant. Improved glycemic control can yield a 10 to 15 % decrease in LDL-C concentrations, lower triglyceride levels and produce a favourable change in the composition of LDL-C particles [28].

Given the already increased risk of cardiovascular disease in diabetes, the association between glycemic control and lipid levels reinforces that cardiovascular health requires an optimization of dyslipidemia in addition to correction for the hyperglycemia.

Studies have shown that diabetes mellitus is a progressive disorder which cannot be effectively managed with drug monotherapy. Regardless of drug management, the pancreatic β-cells in type 2 diabetic patients continue to deteriorate leading to worsening glycemic control and consequent requirement for multiple therapies or exogenous insulin [29]. The mechanisms of action of glibenclamide and metformin are well documented [30, 31]. Glibenclamide belongs to sulfonylurea drug group and is a insulin secretagogue acting on β-cell of islets of Langerhans in pancreas. Metformin belongs to the biguanide class of antidiabetic drugs and works by increasing the activity of AMP dependent protein kinase (AMPK) in multiple tissues. It suppresses the gluconeogenesis in liver, enhances the insulin sensitivity and peripheral utilization of glucose by phosphorylating GLUT-4 enhancer factor [32]. It also increases fatty acid oxidation and thus improves dyslipidemia. By helping in decreasing the total glycemic load and by improving the lipid profile, metformin reduces the overall risk of complications of diabetes mellitus. UKDPS [30] has shown that ten years of metformin treatment reduced diabetes complications and overall mortality by about 30 % when compared with sulfonylureas or even insulin.

Our results have emphasised this role of metformin in the overall management of type 2 diabetes mellitus. Addition of metformin to the regimen improved the glycemic control reflected in decreased glycosylated haemoglobin and was also found to decrease the total and LDL-cholesterol and increase the HDL-cholesterol (albeit non-significantly). Pfutzner et al. [6] conducted a double blind study on 288 type 2 diabetes patients put on two metformin combinations, viz., with glimepiride (next generation insulin secretagogue) and with pioglitazone (stimulator of PPAR-γ). They reported an increase in HDL cholesterol in both the groups along with significant improvement in trigylcerides, HBA1c and blood glucose. The pioglitazone with metformin was more effective on increasing the HDL cholesterol than glimepiride plus metformin.

With the advent of newer management strategies including thiazolidinediones to regulate the downstream insulin sensitivity and the increasing confidence in the safe use of statins to lower the plasma cholesterol, the type 2 diabetes mellitus is progressing towards better management and brighter outcomes. The decreasing cardiovascular risk observed in a number of international drug trials emphasises the increasing role of combination therapy in the management of diabetes mellitus.

Conclusions and Recommendations

Majority of the type 2 diabetes mellitus patients in Africa do not maintain a good glycemic control. Diabetic dyslipidemia characterized by high plasma triglycerides, high LDL-cholesterol and low HDL-cholesterol is tightly associated with glycemic control.

Good glycemic control could result in improvement in the lipid profile and the patients could be spared from the high cardiovascular risk. Combination therapy is better than mono-therapy in controlling the glycemic load in type 2 diabetes mellitus. Metformin added to the other hypoglycemic drugs gives added benefit in the form of reduced glycemic load and improvement in the lipid profile.

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